

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

M

To:
PAMELA J. SHERWOOD
BOZICEVIC, FIELD & FRANCIS LLP
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MENLO PARK, CA 94025

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JAN 14 2005

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

| | |
|---|--|
| Applicant's or agent's file reference GTIN-021WO | Date of mailing (day/month/year) 07 JAN 2005 |
| International application No. PCT/US04/11622 | International filing date (day/month/year) 15 April 2004 (15.04.2004) |
| Applicant NOVARTIS AG | |

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:
 The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 740 14 35

For more detailed instructions, see the notes on the accompanying sheet.
2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.
4. **Reminders**

 Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

 The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

 Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

 In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

 See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

| | |
|--|--|
| Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230 | Authorized officer Brian Whiteman <i>Jean Proctor</i> Paralegal Specialist Telephone No. (703) 308-0196 |
|--|--|

Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|---|--|
| Applicant's or agent's file reference GTIN-021WO | FOR FURTHER ACTION <div style="float: right; font-size: small;">see Form PCT/ISA/220 as well as, where applicable, item 5 below.</div> | |
| International application No. PCT/US04/11622 | International filing date (<i>day/month/year</i>) 15 April 2004 (15.04.2004) | (Earliest) Priority Date (<i>day/month/year</i>) 15 April 2003 (15.04.2003) |
| Applicant NOVARTIS AG | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).



With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (See Box No. III)

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____



as suggested by the applicant.



as selected by this Authority, because the applicant failed to suggest a figure.



as selected by this Authority, because this figure better characterizes the invention.



none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/11622

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

a. type of material



a sequence listing



table(s) related to the sequence listing

b. format of material



in written format



in computer readable form

c. time of filing/furnishing



contained in the international application as filed



filed together with the international application in computer readable form



furnished subsequently to this Authority for the purposes of search

2. ☒

In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/11622

| A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : C12N 15/00, 15/09, 15/63, 15/70, 15/74; C07H 21/02, 21/04 US CL : 435/320.1; 536/23.1 According to International Patent Classification (IPC) or to both national classification and IPC | | | | | | | | | | | | | | | | | | | | |
|---|--|---|--|--|---|--|--|------------|---|--|------------|---|---|--|--|--|--|--|--|--|
| B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 435/320.1; 536/23.1 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet | | | | | | | | | | | | | | | | | | | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category *</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>US 2002/0168771 A1 (GAMERMAN) 14 November 2002 (14.11.02), see whole document especially pages 1 and 8-11.</td> <td>1, 2, 5, 6</td> </tr> <tr> <td>X</td> <td>US 5,874,283 (HARRINGTON et al) 23 February 1999 (23.02.1999), see whole document especially columns 9, 22, 29.</td> <td>1, 2, 3, 5</td> </tr> </tbody> </table> | | | Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. | X | US 2002/0168771 A1 (GAMERMAN) 14 November 2002 (14.11.02), see whole document especially pages 1 and 8-11. | 1, 2, 5, 6 | X | US 5,874,283 (HARRINGTON et al) 23 February 1999 (23.02.1999), see whole document especially columns 9, 22, 29. | 1, 2, 3, 5 | | | | | | | | | |
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. | | | | | | | | | | | | | | | | | | |
| X | US 2002/0168771 A1 (GAMERMAN) 14 November 2002 (14.11.02), see whole document especially pages 1 and 8-11. | 1, 2, 5, 6 | | | | | | | | | | | | | | | | | | |
| X | US 5,874,283 (HARRINGTON et al) 23 February 1999 (23.02.1999), see whole document especially columns 9, 22, 29. | 1, 2, 3, 5 | | | | | | | | | | | | | | | | | | |
| <input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex. | | | | | | | | | | | | | | | | | | | | |
| <table border="0"> <tr> <td colspan="2"> * Special categories of cited documents: </td> <td> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention </td> </tr> <tr> <td> "A" document defining the general state of the art which is not considered to be of particular relevance </td> <td> "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone </td> <td></td> </tr> <tr> <td> "E" earlier application or patent published on or after the international filing date </td> <td> "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art </td> <td></td> </tr> <tr> <td> "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) </td> <td> "&" document member of the same patent family </td> <td></td> </tr> <tr> <td> "O" document referring to an oral disclosure, use, exhibition or other means </td> <td></td> <td></td> </tr> <tr> <td> "P" document published prior to the international filing date but later than the priority date claimed </td> <td></td> <td></td> </tr> </table> | | | * Special categories of cited documents: | | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention | "A" document defining the general state of the art which is not considered to be of particular relevance | "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone | | "E" earlier application or patent published on or after the international filing date | "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art | | "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" document member of the same patent family | | "O" document referring to an oral disclosure, use, exhibition or other means | | | "P" document published prior to the international filing date but later than the priority date claimed | | |
| * Special categories of cited documents: | | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention | | | | | | | | | | | | | | | | | | |
| "A" document defining the general state of the art which is not considered to be of particular relevance | "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone | | | | | | | | | | | | | | | | | | | |
| "E" earlier application or patent published on or after the international filing date | "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art | | | | | | | | | | | | | | | | | | | |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" document member of the same patent family | | | | | | | | | | | | | | | | | | | |
| "O" document referring to an oral disclosure, use, exhibition or other means | | | | | | | | | | | | | | | | | | | | |
| "P" document published prior to the international filing date but later than the priority date claimed | | | | | | | | | | | | | | | | | | | | |
| Date of the actual completion of the international search 25 October 2004 (25.10.2004) | | Date of mailing of the international search report 07 JAN 2005 | | | | | | | | | | | | | | | | | | |
| Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230 | | Authorized officer Brian Whiteman Telephone No. (703) 308-0196 <i>Jean Proctor</i> Paralegal Specialist | | | | | | | | | | | | | | | | | | |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/11622

Continuation of B. FIELDS SEARCHED Item 3:

WEST 2.1, STN

search terms: FEN1, TRE, transcriptional response element, transcriptional regulatory element, adenovirus, TERT, E2F, PRL-3, IRES, ADP, flap

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
PAMELA J. SHERWOOD
BOZICEVIC, FIELD & FRANCIS LLP
200 MEDDLEFIELD ROAD, SUITE 200
MENLO PARK, CA 94025

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

| | | |
|---|--|---|
| Applicant's or agent's file reference GTIN-021WO | | Date of mailing (day/month/year) 07 JAN 2005 FOR FURTHER ACTION See paragraph 2 below |
| International application No. | International filing date (day/month/year) | Priority date (day/month/year) |
| PCT/US04/11622 | 15 April 2004 (15.04.2004) | 15 April 2003 (15.04.2003) |
| International Patent Classification (IPC) or both national classification and IPC | | |
| IPC(7): C12N 15/00, 15/09, 15/63, 15/70, 15/74; C07H 21/02, 21/04 and US Cl.: 435/320.1; 536/23.1 | | |
| Applicant | | |
| NOVARTIS AG | | |

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| | |
|--|--|
| Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230 | Authorized officer Brian Whiteman Telephone No. (703) 308-0196 <div style="text-align: right;"> <i>Jean Proctor</i> Paralegal Sr. </div> |
|--|--|

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US04/11622

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☒ in written format

☒ in computer readable form

c. time of filing/furnishing

☒ contained in international application as filed.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/11622

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------------------|-----|
| Novelty (N) | Claims <u>4, 7-32</u> | YES |
| | Claims <u>1-3, 5, 6</u> | NO |
| Inventive step (IS) | Claims <u>4, 7-32</u> | YES |
| | Claims <u>1-3, 5, 6</u> | NO |
| Industrial applicability (IA) | Claims <u>1-32</u> | YES |
| | Claims <u>NONE</u> | NO |

2. Citations and explanations:

Claims 1, 2, 3, and 5 lack novelty under PCT Article 33(2) as being anticipated by US 5,874,283. HARRINGTON teaches compositions comprising human FEN-1 endonucleases and functional fragments thereof.

Claims 1, 2, 5 and 6 lack novelty under PCT Article 33(2) as being anticipated by US 2002/0168771. GAMERMAN teaches compositions comprising an adenoviral vector comprising a FEN-1 gene.

Claims 1, 2, 3, and 5 lack an inventive step under PCT Article 33(3) as being obvious over US 2002/0168771. GAMERMAN teaches compositions comprising an adenoviral vector comprising a FEN-1 gene.

Claims 1, 2, 5, and 6 lack an inventive step under PCT Article 33(3) as being obvious over US 5,874,283. HARRINGTON teaches compositions comprising human FEN-1 endonucleases and functional fragments thereof.

Claims 4 and 7-32 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an isolated nucleic acid comprising SEQ ID NO: 1.

Claims 1-32 meet the criteria set out in PCT Article 33(4), and thus meet industrial applicability because the subject matter claimed can be made or used in industry the isolated nucleic acid can be used for treating cancer cells.